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Radiographic findings and Gs-alpha bioactivity studies and mutation screening in acrodysostosis indicate a different etiology from pseudohypoparathyroidism

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Abstract Acrodysostosis is an uncommon skeletal dysplasia associated with nasal hypoplasia, midface deficiency, severe brachydactyly, and varying degrees of hearing loss and mental retardation. Previous publications have suggested that it may be difficult to distinguish acrodystostosis from pseudohypoparathyroidism on clinical grounds, but acrodysostosis does appear to have distinct clinical and radiologic findings. Spinal stenosis is an underappreciated risk in acrodysostosis, despite the reported loss of normal caudal widening of the lumbar interpediculate distance on AP spine radiographs in the original report of this disorder by Robinow et al., with confirmation of these radiographic findings by Butler et al. We report two sporadic cases of acrodysostosis, one of which required decompressive laminectomy for symptomatic spinal stenosis, and review 11 cases of acrodysostosis from 9 families that were submitted to the International Skeletal Dysplasia Registry. The objective of this report is to determine the frequency and severity of spinal stenosis in patients with acrodysostosis and to summarize the clinical and radiographic findings of acrodysostosis in an effort to distinguish acrodysostosis clearly from pseudohypoparathyroidism. The pattern of brachydactyly differs between these two conditions, and varying degrees of spinal stenosis are characteristic of acrodysostosis. Both our index patients with acrodysostosis had normal bioactivity of the alpha subunit of the Gs protein, therefore indicating that acrodysostosis has a different pathogenesis from pseudohypoparathyroidism. Furthermore, single-strand confirmational polymorphism (SSCP) analysis failed to demonstrate any confirmational alterations in the coding exons of the Gs alpha gene. These radiographic and laboratory findings substantiate that acrodysostosis is clinically different from pseudohypoparathyroidism and that it is necessary to follow patients with acrodysostosis for signs of spinal stenosis.

Introduction

Acrodysostosis is a rare skeletal dysplasia associated with nasal hypoplasia, midface deficiency, severe brachydactyly, and varying degrees of hearing loss and mental retardation. In 1993, Hamanishi et al. [1] reported a 35-year-old woman with acrodysostosis and numbness in her right arm and both legs, along with intermittent claudication and low back pain. She had moderately severe mental retardation and was the youngest child of older parents at the time of her birth (father 45 and mother 39). She had a history of short, irregular menstruation. Radiographs were typical for acrodysostosis, and because of her history of extremity numbness with weakness on examination, and radicular symptoms which were aggravated on walking and re-

lieved by rest, spinal stenosis was suspected. On spinal radiographs, the sagittal diameter of the lower cervical cord was narrowed, and the normal caudal widening of the lumbar interpedicular distance was lost at L5. CT and MRI confirmed 30–50 % narrowing of the spinal canal, a finding similar to that commonly seen in achondroplasia, but she refused laminectomy. Despite the reported loss of normal caudal widening of the lumbar interpediculate distance on AP spine radiographs in the original report of this disorder by Robinow et al. [2], with confirmation of these radiographic findings in 75 % of the acrodysostosis cases reviewed by Butler et al. [3], until Hamanishi's 1993 report, there were no reports of symptomatic individuals.

We report a similarly affected 14-year-old boy with acrodysostosis, narrowed interpediculate distances in his lumbar spine, neurological symptoms including spinal claudication symptoms, and extensive spinal stenosis by MRI. He underwent decompressive laminectomy with good results. We have also seen a second, younger child who is asymptomatic with severe spinal narrowing and acrodysostosis. Our experience with the unique radiographic features of these two cases, which both had had normal bioactivity of the Gs alpha subunit and no detectable mutations in the coding exons of the Gs alpha gene, prompted us to review 13 cases submitted to the International Skeletal Dysplasia Registry to determine the frequency and severity of spinal stenosis in patients with acrodysostosis. We also reviewed the pattern of brachydactyly among these cases of acrodysostosis and found it to be distinctive and helpful in distinguishing acrodysostosis from pseudohypoparathyroidism (also termed Albright's hereditary osteodystrophy).

Case reports

Case 1

JH was the small-for gestational-age (SGA) product of a term pregnancy complicated by oligohydramnios, born to a 25-year-old G2P1 → 2 woman and her 28-year-old husband. At birth he weighed 2,200 g with a length of 48 cm. He presented with hypoproteinemia and hyponatremia of unknown etiology, both of which resolved spontaneously. After birth, he was noted to be dysmorphic with maxillonasal hypoplasia and brachydactyly. Congenital hypothyroidism was diagnosed on routine prenatal screening; he was started on thyroid supplementation, and further evaluation revealed a hypoplastic thyroid gland. He was also noted to have dextrocardia at birth, with chronic sinusitis requiring prophylactic antibiotics, and a ciliary biopsy suggested ciliary immotility, which led to a diagnosis of Kartagener's syndrome. At age 3, he was fitted with hearing aids for a mixed conductive and sensorineural hearing loss, and he underwent orchiopexy for an undescended right testis.

At age 5, he had surgery for a hip disorder thought to be Legg-Perthes disease, and he wore a hip spica cast for almost 1 year. Upon removal of the cast, he was noted to have bilateral deep vein thromboses, which were treated with anticoagulants. A protein S-level suggested mildly decreased activity, but not in the range one would expect with a dominant protein S deficiency. He was followed for his findings of maxillonasal hypoplasia, brachydactyly (Fig. 1), radioulnar synostosis, and mildly delayed development. Radiographs at age 9 years were consistent with acrodysostosis. Hands revealed generalized brachydactyly, especially digits 2–5, which was most severe in metacarpals, with fused epiphyses and residual coned epiphyses in the proximal phalanges. There was marked shortening of middle and distal phalanges, with residual cones, and thumbs were relatively spared. The feet showed similar severe shortening of digits 2–5, with relative sparing of the halluces, and the skull showed moderately severe midface hypoplasia (Fig. 2). Spine radiographs revealed lumbar spinal stenosis.

At age 14 years, height was in the 25th-50th centile, weight 90th centile and head circumference 50th centile. He presented with worsening orthopedic problems, including limited flexibility in the hips and marked difficulty reaching down to tie his shoes or pick items up from the floor. He complained of pain and weakness in his legs when walking, characteristic of spinal claudication symptoms. He demonstrated lower extremity hyperreflexia with asymmetrical deep tendon reflexes. His gait was abnormal with Trendelenburg gait on the left. He was thought to have had worsening of his spinal stenosis as a consequence of his 35–40 ° hip flexion contracture, which resulted in increased lumbar lordosis when walking, consequently decreasing the volume in his lumbar spinal canal. Spinal MRI demonstrated diffuse spinal stenosis (Fig. 3), and he underwent laminectomy from T12 to L5, with good relief of his neurological symptoms. Following the laminectomy, he had a normal postoperative renal and bladder ultrasound, with normal flow versus volume voiding and normal urinary residual volume.

His karyotype was normal, and telomeric markers from the chromosome 2q37 region showed the presence of bi-allelic inheritance, excluding a deletion of 2q37 as an etiology for his phenotype. This experiment was performed because Wilson et al. [4] had reported that patients with chromosome 2q37 deletions have associated brachydactyly, mental retardation, and an Albright hereditary osteodystrophylike syndrome. Since previous authors had speculated that acrodysostosis and pseudohypoparathyroidism shared a common pathogenesis, we analyzed erythrocyte Gs alpha bioactivity and found normal levels of activity. Furthermore single-strand confirmational polymorphism (SSCP) analysis failed to demonstrate any confirmational alterations in the coding exons of the Gs alpha gene [5].

Case 2

UZ was the SGA product of an uncomplicated vertex vaginal delivery to a 38-year-old G2P1 → 2 woman and her 42-year-old husband. At birth the baby weighed 2,000 g and measured 49.5 cm. He was found to be hypothyroid and started on thyroid replacement from age 1 week to 3 years, at which time his thyroid function had normalized. Thyroid replacement was discontinued, and he has remained euthyroid. At 4 years of age he was referred for ysmorphic features with speech delay and was noted to have maxillonasal hypoplasia, brachydactyly (Fig. 4), and developmental delay, particularly affecting his speech development. Height and weight were at the 75th centile, with head circumference at the 25th centile. A skeletal survey was consistent with acrodysostosis, the spine showing lack of the normal lumbar interpediculate flare, hands and feet revealing generalized brachydactyly, especially digits 2–5, metacarpals with coned epiphyses and early fusion, proximal phalanges 2–5 demonstrating residual cones with fusion, and middle and distal phalanges 2–5 showing no residual cones, but severe shortening, with relative sparing of thumbs and halluces (Fig. 5).

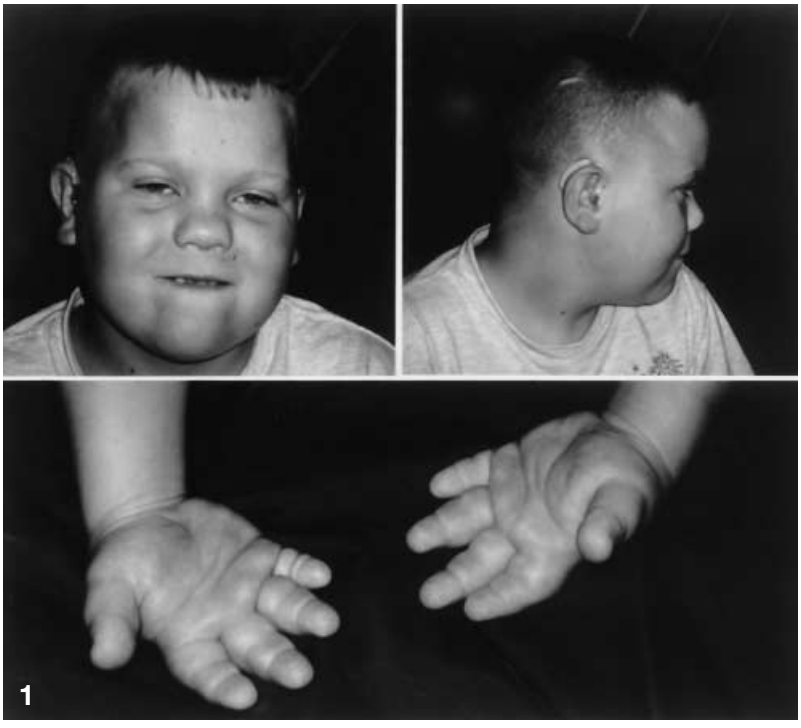

Fig. 1 Facial features and hands of case 1 at age 9 years, showing maxillonasal hypoplasia and brachydactyly

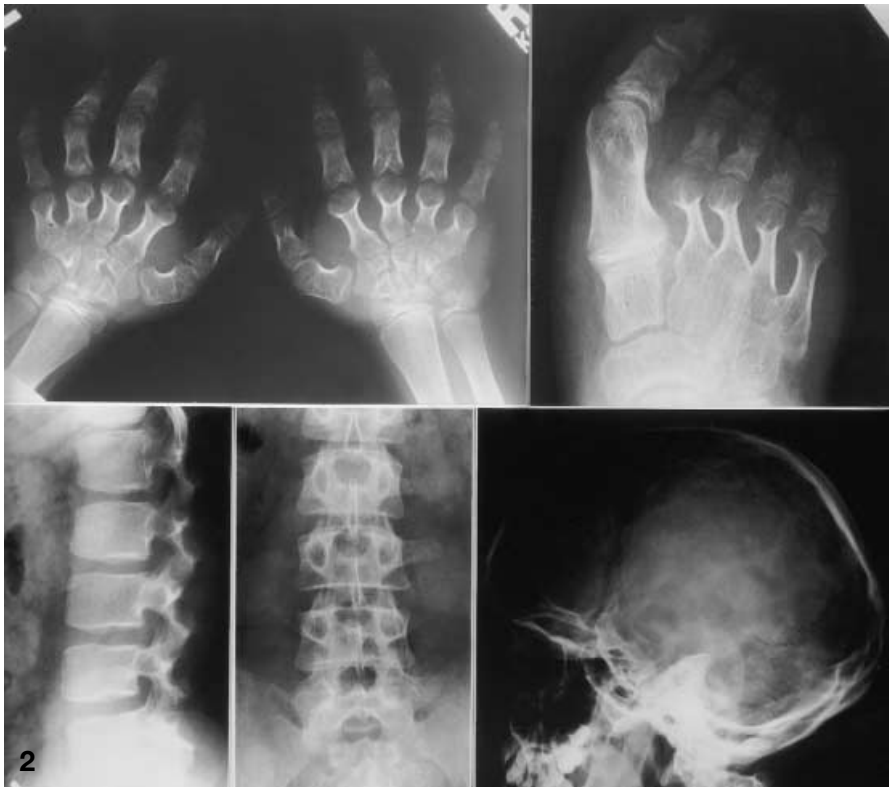

Fig. 2 Radiographs from case 1 at 9 years of age. *Hands* Generalized brachydactyly, especially digits 2–5; most severe in metacarpals with fused epipyses; residual coned epiphyses in proximal phalanges; marked shortening middle and distal phalanges, residual cones; thumbs spared. *Foot* Similar severe shortening of digits 2–5, with relative sparing of halluces. *Spine* Lumbar spinal stenosis evident on AP and lateral views. *Skull* Typical moderately severe midface hypoplasia

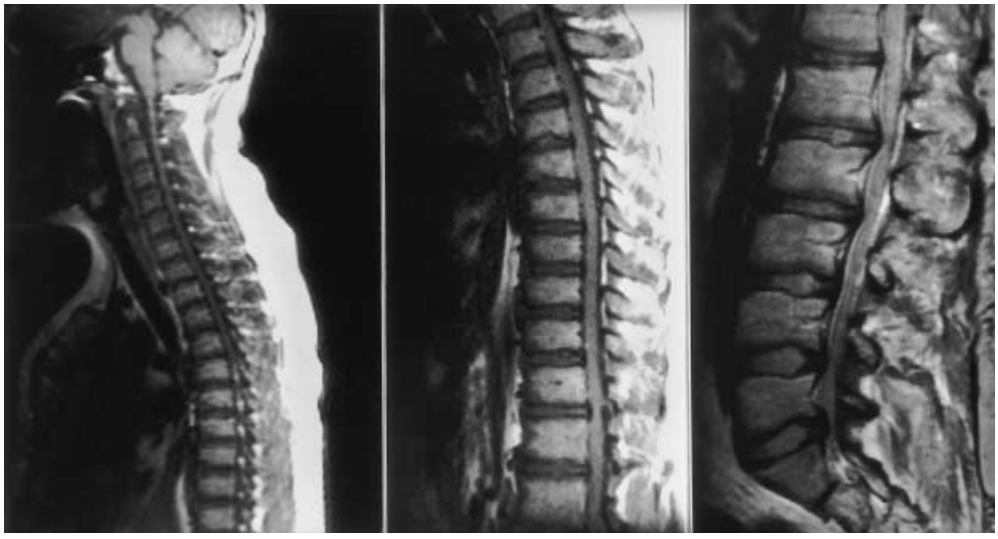

Fig. 3 Lumbosacral sagittal spinal MRI of case 1 at 14 years of age, demonstrating diffuse lumbar spinal stenosis

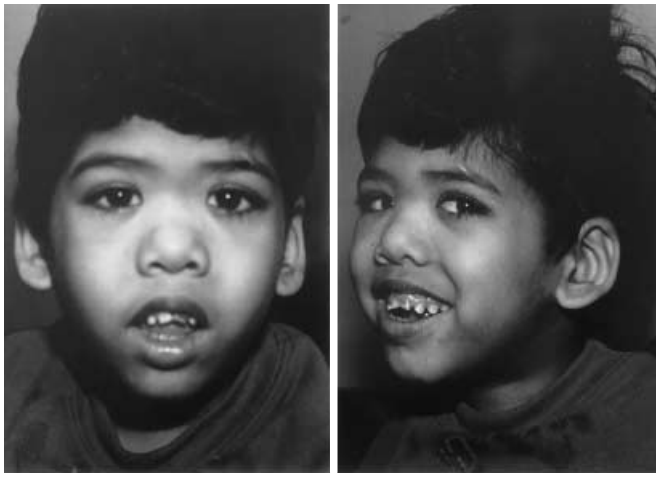

Fig. 4 Facial features of case 2 at age 4 years, showing maxillonasal hypoplasia

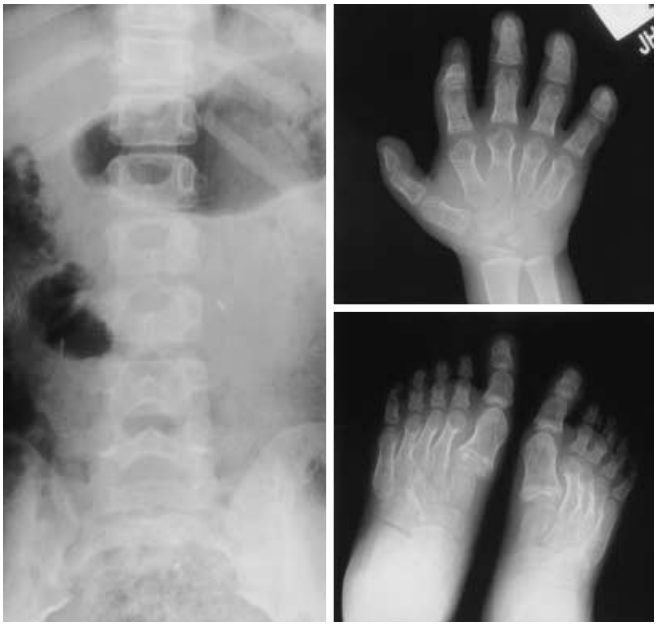

Fig. 5 Radiographs from case 2 at 4 years of age. *Spine* Lack of normal lumbar interpediculate flare. *Hands/Feet* Generalized brachydactyly, especially digits 2–5. Metacarpals: coned epiphyses with fusion; proximal phalanges 2–5: residual cones with fusion; middle and distal phalanges 2–5: no residual cones, but severe shortening; sparing thumbs and halluces

Karyotype was normal, and use of telomeric markers for 2q37 failed to reveal any deletion. Studies of erythrocyte Gs alpha bioactivity were normal and no sequence variation of the Gs-alpha gene was identified by SSCP analysis [5].

Methods

Blood was obtained with Institutional Review Board consent from patients JH and UZ, and their respective parents. For measurement of Gs alpha bioactivity, approximately 5 ml of venous blood was collected in citrate anticoagulant, frozen on dry ice, and stored appropriately. Dr. C. van Dop kindly measured the erythrocyte Gs alpha activity. Values of cAMP activity for JH and UZ were 30 pmol and 20 pmol, respectively, and were in the normal range relative to the general population and to their parents who were also used as controls.

Genomic DNA was extracted from peripheral lymphocytes using standard methods. Exons 1–13 of the Gs alpha gene were screened by SSCP [6] gel electrophoresis. No detectable changes were noted in the exons of the two patients tested.

Registry radiographic analysis

Based on the clinical and radiographic findings in these two patients with acrodysostosis and normal erythrocyte Gs alpha bioac-

tivity and no sequence variation of the Gs-alpha gene, radiographs and clinical histories on 11 other patients from 9 families that had been submitted to the International Skeletal Dysplasia Registry were examined for similar features. The goal was to determine the frequency and severity of spinal stenosis and to determine if the pattern of brachydactyly could discriminate this condition from other skeletal dysplasias and dysostoses. The clinical and radiological features of these 11 cases are described briefly below, arranged from youngest to oldest patients, at the time their radiographs were taken.

Case R1

SC was delivered at 37 weeks by cesarean section to a 29-year-old primagravida because of intrauterine growth retardation and oligohydramnios. During the pregnancy, his mother had used a Mexican beauty cream containing mercury and was found to have toxic blood levels of mercury, so chelation therapy was undertaken. At birth, the baby boy weighed 1,800 g and was noted to have small hands and feet with marked midface deficiency. He was found to be developmentally delayed, particularly for speech. At 5 years of age he underwent nasal reconstruction with tonsilectomy and adenoidectomy. He demonstrated maxillonasal hypoplasia with generalized brachydactyly, and skull and hand radiographs were consistent with acrodysostosis. A cranial MRI was normal with views of the cervical cord showing no cervical cord stenosis. Spinal radiographs revealed lack of the normal lumbosacral interpediculate widening in the lower lumbosacral area. Chromosome analysis was normal.

Case R2

AD was the SGA 2,500-g product of a planned C-section delivery for previous C-section, born to a 24-year-old G2P1 ≥ 2 mother. At 2 years of age she was evaluated for growth deficiency and given the diagnosis of peripheral dysostosis. She had no other known medical problems, graduated from college and works as a financial analyst, with an adult height at the third centile. The family history is significant for mildly short stature among her mother and maternal aunts and uncles, with their adult heights ranging from the third to tenth centile. She had radiographs taken at 4 and 7 years. Hands revealed brachydactyly with more severe involvement of metacarpals than is usually seen in this disorder. There were coned epiphyses in metacarpals, proximal and middle phalanges of digits 2–5, with spine radiographs revealing lack of lumbosacral interpediculate flare, and a skull revealing moderate midface hypoplasia.

Case R3

PM was induced at 37 weeks because of intrauterine growth retardation. At 5 years, his height age was 3 years, and his head circumference was 25th centile. He had a flat nasal bridge with epicanthal folds, limited elbow extension, and small hands with short fingers and short toes. He was delayed in his speech with fine motor problems, and skeletal survey suggested a diagnosis of acrodysostosis. Spine radiographs demonstrated lack of normal lumbar interpediculate flare, while hands showed generalized brachydactyly, especially digits 2–5, with metacarpals most severely affected, and revealing fusing coned epiphyses. Proximal phalanges revealed short, residual fused cones, and middle and distal phalanges were very short, with no residual cones. There was relative sparing of the thumbs.

Cases R4 A, B, C

This family consists of a mother and her two sons, all three of whom are affected with acrodysostosis and required operative intervention for stenosis of the cervical spinal cord due to a tight foramen magnum. The mother (SC) had surgery for "foramen magnum stenosis," culminating in a shunt for hydrocephalus at 18 years of age. Her adult height was just below the 10th centile, and she had small hands and feet with short digits, flat nasal bridge, midface deficiency, and a prognathic-appearing jaw. Her mother was said to have similar facial and digital findings, but with no known spinal complications. Her two sons required decompressive cervical laminectomies for cervical cord stenosis at the level of and just below the foramen magnum. At 8 years, 8 months, the younger son (SC) was 25th-50th centile for height with a 95th centile head circumference, and he had recently undergone a decompressive cervical laminectomy with shunting for hydrocephalus and some spasticity. Her older son (NC) was seen and operated on at age 9 years, 8 months, and had been rendered quadriplegic due to cervical cord stenosis, requiring a wheelchair for mobility. His length was just below the 10th centile. All three affected family members had normal calcium and phosphate levels. Both boys had chronic otitis media with maxillonasal growth deficiency, epicanthal folds, and relative prognathism. Hand radiographs in the mother demonstrated severe shortening of metacarpals, while her sons had mild brachydactyly with coned epiphyses in the metacarpals (Fig. 6).

Case R5

SH was the normal-sized product of a term pregnancy; he was evaluated at age 16 years for short stature and learning disabilities with normal hearing and a normal karyotype. His height was 3 standard deviations below the mean for age, and he had a flat nasal bridge, small hands with 5th finger clinodactyly, small 5th toes, and a normal neurological exam. Based on the selective pattern of involvement, radiographs suggested a diagnosis of mild acrodysostosis, with hands revealing generalized brachydactyly, involving the metacarpals, middle, and distal phalanges of digits 2–5. The spine revealed a lack of the normal lumbosacral interpediculate flare.

Case R6

OV was evaluated at age 18 years for short stature with learning disabilities. Her karyotype was normal, and she was treated for hypothyroidism because of low T4 and elevated TSH. She had secondary amenorrhea, her parathyroid hormone level was normal, and her height was less than the 3rd centile. She had a flat nasal bridge with marked brachydactyly, and a skeletal survey suggested a diagnosis of acrodysostosis with brachydactyly that was more severe in her metacarpals, where previously coned epiphyses had fused. She also had interpediculate narrowing of her lumbosacral spine and complained of intermittent numbness in the fingers of her left arm.

Case R7

CS was a 19-year-old woman referred for brachydactyly with spinal stenosis. Radiographs suggested a diagnosis of acrodysostosis, with hands revealing generalized brachydactyly, especially affecting the metacarpals, with fused, previously coned epiphyses,and relative sparing of the thumbs. Her spine showed significant lumbar interpediculate narrowing.

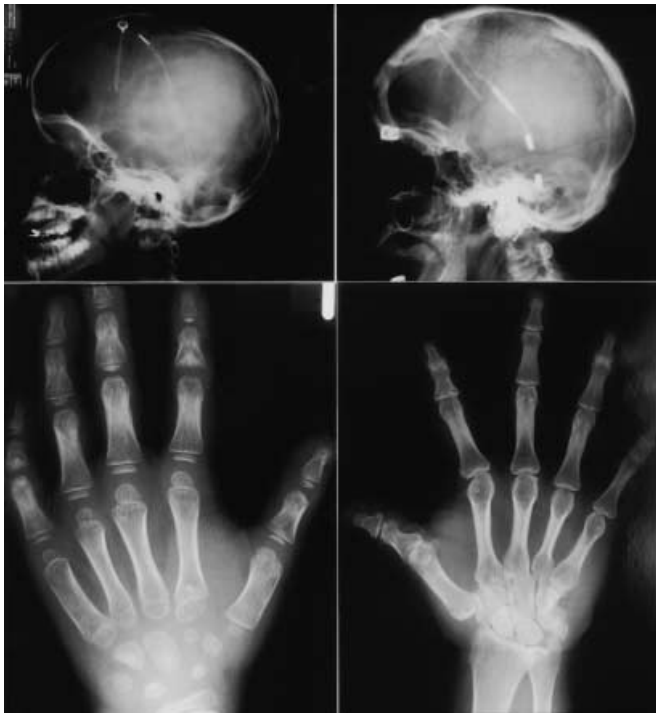

Fig. 6 Registry cases R4 A, B: 8-year-old boy on left; mother on right. *Skull* Severe midface hypoplasia with hydrocephalus foramen magnum stenosis s/p cervical laminectomy. *Hand* Mild brachydactyly with coned epiphyses in son Brachymetacarpaly in mother is more severe

Case R3

SL is a 27-year-old woman, with proportionate short stature, marked brachydactyly, and mild contractures of the elbows. Her 2.5-month-old infant had a length and weight below the 3rd centile with a 50th-centile head circumference, short nose, and mild shortening of extremities with short fingers. Calcium, phosphorus and parathyroid hormone levels were all normal. Radiographs on the mother suggested a diagnosis of acrodysostosis, with generalized brachydactyly and severe phalangeal and metacarpal shortening. Spine films demonstrated lumbosacral interpediculate narrowing and spinal stenosis (Fig. 7).

Case R9

DL was a 30-year-old female referred for short stature, small hands and feet, and shunted hydrocephalus due to a "small foramen magnum." Radiographs suggested a diagnosis of acrodysostosis with generalized brachydactyly, and relative sparing of thumbs and halluces (Fig. 8).

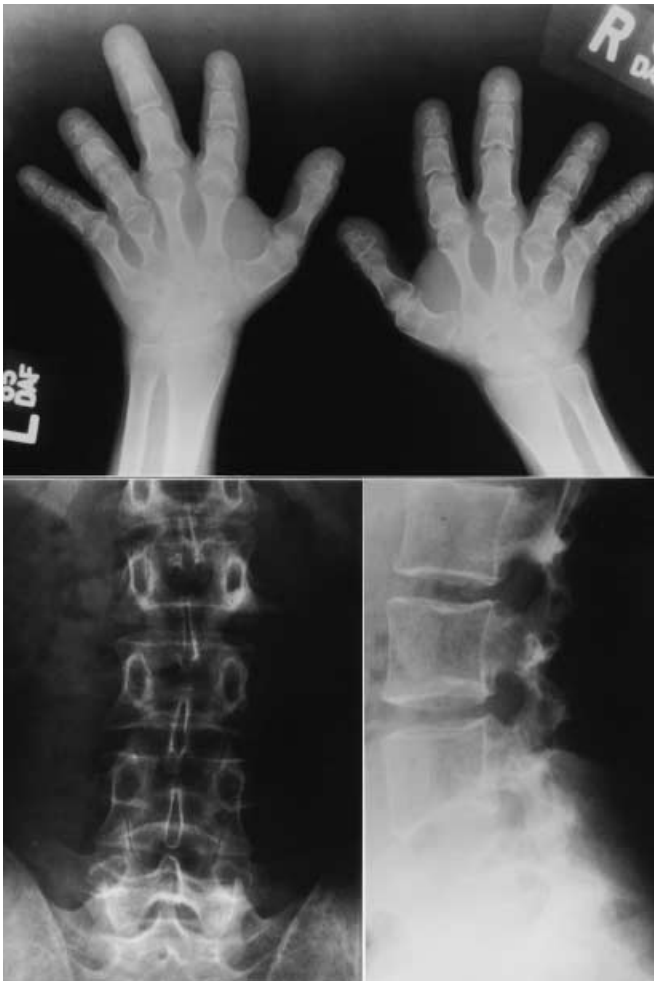

Fig. 7 Registry case R8: 27-year-old woman, with brachydactyly; phalangeal shortening just as severe as metacarpals. L-S interpediculate narrowing and lumbar spinal stenosis on AP and lateral views

Discussion

Acrodysostosis is a syndrome that results in marked nasal hypoplasia with midface deficiency and relative prognathism. There is associated brachydactyly with coned epiphyses affecting metacarpals as well as phalanges, and relative sparing of thumbs and halluces, which makes them appear relatively long in adulthood. There is variable intrauterine growth deficiency, developmental delay, learning disability, limitation to elbow movements, and hearing loss, and most patients demonstrate short stature as adults. Some patients also manifest hypothyroidism. Because of the brachydactyly, learning problems, and short stature, acrodysostosis has previously been considered to be clinically indistinguishable from pseudohypoparathyroidism [7]. Acrodysostosis was initially thought to have a similar but more severely affected pattern profile analysis to that in pseudohypoparathyroidism [8], but as more cases of acrodysostosis were studied, a characteristic pattern emerged for acrodysostosis [3]. This pattern is demonstrated in Figs. 2 and 5–8.

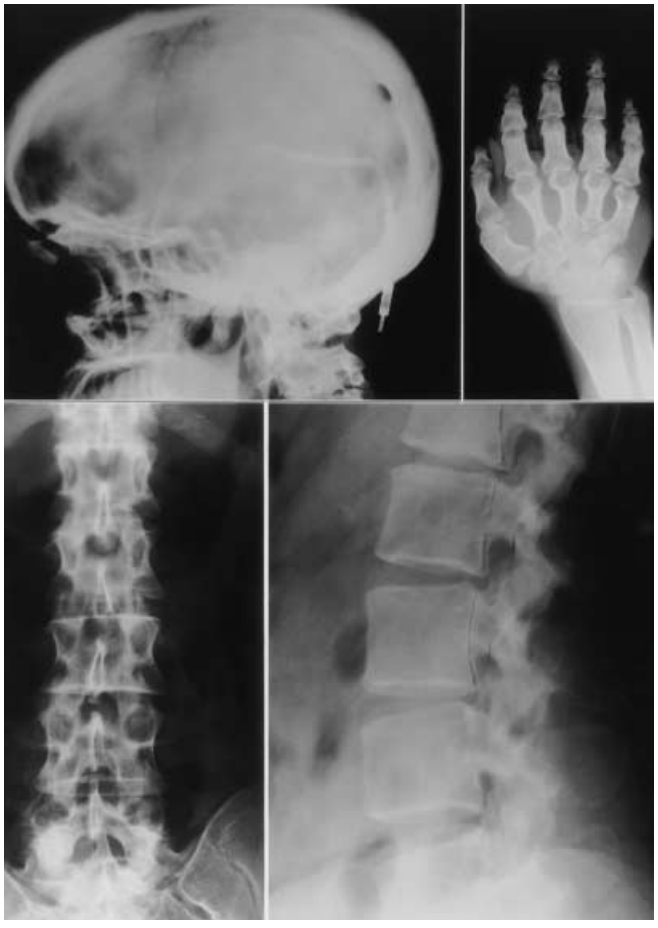

Fig. 8 Registry Case R9: 30-year-old woman with short stature. *Skull* Severe midface hypoplasia, with shunted hydrocephalus due to small foramen magnum. *Hands/feet* Generalized brachydactyly, more severe in metacarpals digits 2–5; thumb relatively spared. *Spine* Interpediculate narrowing on AP and lateral lumbar views

Our series of 13 cases demonstrates that spinal stenosis is common in acrodysostosis, with 5 of our patients requiring decompressive laminectomies, and all patients with available radiographs demonstrating lack of the usual lumbosacral interpediculate widening in the lower spine. Such problems are usually not seen with documented pseudohypoparathyroidism. The frequency and magnitude of spinal stenosis in patients with acrodysostosis are similar to what is seen in patients with achondroplasia, and therefore, spinal cord symptoms in patients with acrodysostosis must be further evaluated for clinical and radiographic signs of spinal stenosis. When hip flexion contractures are present, it is more likely that the spinal stenosis will become symptomatic and require surgical intervention with laminectomy.

Acrodysostosis was initially delineated by Robinow et al. [2]. They noted a distinctive type of brachydactyly in all 20 cases, emphasizing the associated features of short stature, flat nasal bridge, malocclusion, and mental retardation. One of their initial patients had hydrocephalus, and six had hearing loss. Several cases had incomplete sexual maturation or cryptorchidsm and nine cases lacked normal lumbosacral widening on spine films. All cases were sporadic, with a mean maternal age of 28, and a mean paternal age of 35, which suggested the possibility of a fresh dominant mutation. Parent-to-child transmission of acrodysostosis in two of our families confirms this suspicion, and there are other similar reports in the literature [9–12].

Because shortening of the tubular bones in the hands and feet with coned epiphyses can be seen in both acrodysostosis and pseudohypoparathyroidism (Albright's hereditary osteodystrophy), these two disorders have frequently been confused. It is now known that the underlying defect in pseudohypoparathyroidism is a reduction in the bioactivity of the alpha subunit of the signal transducing protein, Gs, due to heterozygous deactivating mutations in the Gs alpha gene on chromosome 20q13 [13–15]. The signal transducing protein, Gs, stimulates intracellular adenyl cyclase in response to various peptide hormones. Our two index cases of acrodsysostosis have normal erythrocyte membrane Gs bioactivity, with no evidence for sequence variation in the Gs alpha gene [5]. Furthermore, their karyotypes were normal, and telomeric markers from chromosome 2q37 failed to reveal any deletion of this chromosomal region that had previously been associated with brachydactyly, mental retardation, and an Albright hereditary osteodystrophylike syndrome [4]. A recent study of two other patients with acrodysostosis also demonstrated normal erythrocyte membrane Gs bioactivity with no sequence variations found in the Gs alpha gene on denaturing gradient gel electrophoresis [16]. These findings suggest that acrodysostosis is distinct from pseudohypoparathyroidism, with no evidence that the two disorders are allelic.

Butler et al. [3] reported a 13-year-old boy with acrodysostosis and reviewed 30 previously reported cases, reporting a characteristic metacarpophalangeal pattern profile for the brachydactyly in acrodysostosis that affected metacarpals 2–5 more severely than the corresponding phalanges and tended to spare the thumbs and halluces. They also noted that 75% of patients with acrodysostosis had vertebral abnormalities, most commonly decreased interpediculate distances. These radiographic features are important distinguishing features that help to differentiate acrodysostosis from pseudohypoparathyroidism.

Ablow et al. [7] reported two unrelated patients who at the time were felt to show features of both acrodysostosis and pseudohypoparathyroidism. In retrospect, their first patient had resistance to parathormone with ectopic calcifications and a flat nasal bridge; this patient

appears to have had pseudohypoparathyroidism, while their second patient had acrodysostosis. The family reported by Davies and Hughes [17] as having familial acrodysostosis appears to have hands and feet that suggest pseudohypoparathyroidism, with the affected father showing minimally elevated parathyroid hormone and mild hypocalcemia. The proband in this family is said to have interpediculate narrowing on spine films. Such cases should be restudied for Gs bioactivity or linkage to 20q13 before concluding that this family has acrodysostosis.

Conclusions

This study demonstrates that spinal stenosis is a symptom of acrodysostosis, since it is present anatomically in early childhood. Most importantly, this finding should alert clinicians to be aware of this association and to examine and study their patients accordingly so as to avoid permanent neurologic sequelae in affected patients. Secondly, on clinical grounds, the finding of spinal stenosis helps to differentiate patients with acrodysostosis from those with pseudohypoparathyroidism. Although only four patients with acrodysostosis have been evaluated for Gs alpha bioactivity or sequence variation in the Gs alpha gene, the negative results in these four cases strongly suggest that acrodysostosis is pathogenetically distinct from pseudohypoparathyroidism.

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